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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,441	12/18/2001	Martin J. Jacobs	CP216	2296

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,441	JACOBS ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/22/05 and interview of 9/21/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CB

DETAILED ACTION

Status of the Claims

Claims 88-98 have been canceled. New claims 99-134 have been added. Any rejection or objection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 99-116, 118, 121-132, and 134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of treating a disease or disorder comprising the administration of a "therapeutically effective" amount of a modafinil/cyclodextrin mixture. However, without knowing what disease is to be treated with the recited agent, it is impossible to determine what is a therapeutically effective amount of said agent.

Claim Rejections - 35 USC § 103

Claims 99-110, 112-120, 126-129, and 131-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over LAFON (US 4,927,855) in view of RAMBERT et al (Neuropharmacology, 1994).

The claims have been amended from compositions to methods of treatment. The new claims are drawn to a method of treating a disease or disorder comprising the administration of a therapeutically effective amount of a modafinil/cyclodextrin mixture. Dependents are drawn to the use of a particular isomer of modafinil, cyclodextrin species, composition form, molar ratios, particular disorders and unit dosages.

LAFON teaches the administration of the levorotatory isomer of benzhydrylsulfinyl acetamide (modafinil) for the treatment of hypersomnia. See abstract. The reference further teaches unit dosages (tablets or capsules) of 50 to 100 mg per day. See col 6, lines 58-61. The reference further notes that the compound is insoluble in water. See Preparation at col 3. The reference does not teach the administration of a modafinil/cyclodextrin mixture or administration of modafinil in a liquid form.

RAMBERT teaches that HP–β–cyclodextrin has utility for solubilizing modafinil. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of LAFON by administering a mixture of modafinil with HP–β–cyclodextrin for the treatment of hypersomnia. The artisan would be motivated to include this component to improve the solubility of the active agent in a physiological environment. One of ordinary skill would reasonably expect success in using HP–β–cyclodextrin for this purpose because LAMBERT had taught that this agent is useful for solubilizing modafinil. In preparing a modafinil/cyclodextrin composition, it would be within the scope of the artisan to optimize the molar ratios of the components to provide a more soluble product. It

would be further obvious to prepare the modafinil/cyclodextrin in the form of a liquid for administration to patients having difficulty with swallowing pills.

Claims 99-110, 112-120, 126-129, and 131-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over LAFON (US 4,927,855) in view of RAMBERT et al (Neuropharmacology, 1994) and further in view of LOFTSSON et al (J. Pharm. Sci., 1996).

The invention is as set forth above.

LAFON and RAMBERT teach as set forth above. The references do not teach the full range of cyclodextrins recited in the claims.

LOFTSSON teaches that a wide variety of cyclodextrins are known for solubilization and increased bioavailability of drugs. See entire reference, especially abstract and Tables 2 and 5. Table 5 establishes that solubilization of a drug with one cyclodextrin can typically be extrapolated to others.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of LAFON by administering a mixture of modafinil with a cyclodextrin for the treatment of hypersomnia. The artisan would be motivated to include this component to improve the solubility of the active agent in a physiological environment. LAMBERT had taught that HP–β–cyclodextrin is useful for solubilizing modafinil, so one of ordinary skill would reasonably expect success in using other cyclodextrins known in the art.

Claims 99-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over LAFON (US 4,927,855) in view of RAMBERT et al (Neuropharmacology, 1994) and further in view of PITHA et al (Int. J. Pharm., 1986).

The invention is as set forth above.

LAFON and RAMBERT teach as set forth above. RAMBERT does not clearly suggest the use of 2–HP–β–cyclodextrin in amounts necessary to produce the high concentrations of modafinil recited in the claims.

PITHA teaches that 2–HP–β–cyclodextrin is highly soluble in water and is useful for solubilizing drugs with limited water solubility. See abstract; Fig. 1; and Table 1. The reference teaches that aqueous solutions comprising up to about 75% (w/w) of 2–HP–β–cyclodextrin can be prepared and that solubilities of some compounds in aqueous 2–HP–β–cyclodextrin (40-50% w/w) are up to three orders of magnitude higher than those in water. See page 79, right column.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the RAMBERT composition using a high concentration of 2–HP–β–cyclodextrin because PITHA had taught that this CD has very high water solubility and has very good solubilizing power for compounds having low water solubility. One of ordinary skill would be motivated to prepare such a composition for administration as taught by LAFON. RAMBERT had already established that HP–β–cyclodextrin was useful for solubilizing modafinil, *per se*, so the artisan would reasonably expect success in preparing such a composition. One of ordinary skill would have been motivated to prepare a concentrated solution in order to minimize the volume of the solution necessary to solubilize the modafinil to be

administered to a patient. In doing so, one of ordinary skill would reasonably expected to attain solutions having the physiological properties set forth in the claims.

Claims 99-101, 103-107, 109, 110, 112-115, 117-120, 126-129, and 131-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over SCAMMELL (US 6,455,588) in view of RAMBERT et al (Neuropharmacology, 1994).

The invention is as set forth above.

SCAMMELL teaches the administration of modafinil for the stimulation of appetite and weight gain. See col 2, lines 10-20. The reference further teaches preferred dosages and composition forms. See col 3, lines 17-30 and col 4, lines 3-19. The reference does not teach the administration of a modafinil/cyclodextrin mixture.

RAMBERT teaches as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of SCAMMELL by administering a mixture of modafinil with HP–β–cyclodextrin to stimulate appetite and promote weight gain. The artisan would be motivated to include this component to improve the solubility of the active agent in a physiological environment. One of ordinary skill would reasonably expect success in using HP–β–cyclodextrin for this purpose because LAMBERT had taught that this agent is useful for solubilizing modafinil. In preparing a modafinil/cyclodextrin composition, it would be within the scope of the artisan to optimize the molar ratios of the components to provide a more soluble product.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 99-101, 103-105, and 117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 16 of U.S. Patent No. 6,455,588 in view of RAMBERT et al (Neuropharmacology, 1994).

Reference claim 16 recites oral administration of modafinil to stimulate appetite and promote weight gain. The reference composition does not recite the use of a cyclodextrin.

RAMBERT teaches as set forth above.

It would have been obvious to modify the method of the reference claim by the administration of a cyclodextrin in combination with modafinil in order to increase solubility of the modafinil as discussed above.

Response to Arguments

Applicant does not present arguments directed at the new rejections. However, Applicant did submit a variety of references for consideration. These references concern the use of cyclodextrins with pharmaceutical products. It appears to be Applicant's position that an increase

in bioavailability of a drug when combined with a cyclodextrin is not predictable, so the increase seen in the instant invention constitutes unexpected results. The examiner respectfully disagrees.

Applicant cites Figure 1 and the concluding paragraphs of WESTERBERG et al (J. Pharm. Sci., 2005). The reference teaches that in the particular experimental conditions disclosed, the bioavailability of benzopyrene (BaP) is reduced by a concurrent dosage of β–cyclodextrin. It is noted that in this case, a dose of BaP is solubilized in ethanol and administered as gastric gavage. A more pertinent comparison would be an orally administered dosage of BaP (without an additional solubilizer) versus a composition comprising BaP and a CD. The bioavailability may still be reduced, but that cannot be determined. It is also noted that this reference states that "natural and modified cyclodextrins ... have found widespread use to improve solubility, chemical and physical stability, and/or bioavailability of drugs ..." See paragraph bridging pages 114-115.

In LOFTSSON (Pharm. Tech., 1999), Applicant cites the section "Cyclodextrin and Membrane Permeability" at page 46. The examiner notes that the reference teaches that the addition of β–cyclodextrin does not automatically increase bioavailability and that it is important to use just enough in the formulation. So essentially the reference teaches that the proper amount of β–cyclodextrin used in a formulation is something that may be optimized by one of ordinary skill with routine experimentation. The examiner further notes that this reference states "Cyclodextrins are *mainly* used to increase the aqueous solubility, stability, and *bioavailability* of drugs ..." (emphasis added) See first paragraph of reference.

In HOSTETLER et al (Antimicrob. Agents Chemother., 1992), Applicant cites Table 1. The table shows that in some cases, a drug may have lower bioavailability when used with a

cyclodextrin than when used with another solubilizer. Again, the more relevant comparison would be cyclodextrin versus no solubilizer.

In NAKANISHI et al (Chem. Pharm. Bull., 1989) Applicant cites the Introduction and Figure 2. The introduction states "β–cyclodextrin ... forms inclusion complexes with various hydrophobic drugs, resulting in the improvement of solubility, dissolution rate, and *bioavailability* of drugs." (emphasis added) It also teaches that if the formation constant of a complex is very large, the addition of β–cyclodextrin may not improve bioavailability. It is the opinion of the examiner that this reference may provide the possible basis for unexpected results. If it were the case that a drug had a very large formation constant, it might be unexpected for it to also have greatly increased bioavailability.

The abstract of SPIRICHEV et al (Vopr. Pitan., 1996) is another case of an apples-to-oranges comparison. The examiner does not find the comparison of beta-carotene with cyclodextrin versus beta-carotene with other solubilizers to be apt, as discussed above.

The foregoing references demonstrate that under some conditions, cyclodextrins may decrease the bioavailability. However, even these references state what is known in the art—the typical intent in using cyclodextrins with hydrophobic drugs is to increase solubility and bioavailability. The fact that this outcome, increased bioavailability, is seen in this case—even though it is not perfectly predictable—does not appear to be the basis for unexpected results.

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

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Leigh C. Maier

Leigh C. Maier
Primary Examiner
November 4, 2005